DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration

21 CFR Part 310

[Docket No. 91N-0505]

RIN 0905-AA06

Status of Certain Additional Over-the-Counter Drug Category II and III Active Ingredients

AGENCY: Food and Drug Administration, HHS.

ACTION: Final rule.

SUMMARY: The Food and Drug Administration (FDA) is issuing a final rule establishing that certain active ingredients in over-the-counter (OTC) drug products are not generally recognized as safe and effective or are misbranded. FDA is issuing this final rule after considering the reports and recommendations of various OTC advisory review panels and public comments on the agency's notices of proposed rulemaking. Based on the absence of substantive comments in opposition to the agency's proposed nonmonograph status for these ingredients, as well as the absence of submissions by interested parties of new data or information to FDA pursuant to the regulations, the agency is issuing this final rule to remove from the OTC market these ingredients for the uses specified in this rule. This final rule is part of the ongoing review of OTC drug products conducted by FDA.

EFFECTIVE DATE: November 10, 1993.

FOR FURTHER INFORMATION CONTACT: William E. Gilbertson, Center for Drug Evaluation and Research (HFD-810), Food and Drug Administration, 5600 Fishers Lane, Rockville, MD 20857, 301-295-8000.

SUPPLEMENTARY INFORMATION: In various issues of the **Federal Register**, FDA has published, under § 330.10(a)(6) (21 CFR 330.10(a)(6)), advance notices of proposed rulemaking to establish monographs for specific classes of OTC drug products, together with the recommendations of the OTC advisory review panels, which were responsible for evaluating data on the active ingredients in the specific drug class(es) in each proposed monograph. Following publication of each proposed monograph, interested parties were invited to submit comments within a set time period, with an additional period of time allowed for reply comments in response to comments filed in the initial comment period.

FDA evaluated the OTC advisory review panels' recommendations and the comments and reply comments received in response to the initial publication of the advance notices of proposed rulemaking. After considering this information, the agency published proposed regulations (in the form of tentative final monographs for various specific classes of OTC drug products). Interested persons were invited to file comments, objections, and/or requests for an oral hearing before the Commissioner of Food and Drugs (the Commissioner) regarding the specific proposals within a set time period. A period of 12 months was provided for the submission of new data and information regarding each specific proposed rulemaking, and 2 additional months were provided for comments on the new data. The publication dates, comment closing dates, and new data closing date for each advance notice of proposed rulemaking and notice of proposed rulemaking are listed in Table I of the August 25, 1992 proposed rulemaking discussed below. (See 57 FR 38568 at 38569.)

In the **Federal Register** of August 25, 1992 (57 FR 38568), FDA published, under § 330.10(a)(7)(ii) (21 CFR 330.10(a)(7)(ii)), a proposed rulemaking encompassing certain Category II and III active ingredients for which the periods for submission of comments and new data following the publication of a notice of proposed rulemaking had closed and for which no significant comments or new data to upgrade the status of these ingredients had been submitted. In each instance, a final rule for the class of ingredients involved had not been published to date. Since that time, final rules for two of the OTC drug rulemakings included in the proposal, external analgesic drug products for diaper rash and topical antifungal drug products for diaper rash, were published on December 18, 1992 (57 FR 60426 and 60430, respectively). Accordingly, the active ingredients from those rulemakings that were included in the proposal are not included in this final rule.

The OTC drug review administrative procedures provide in § 330.10(a)(7)(ii) that the Commissioner may publish a separate tentative order proposing that active ingredients be excluded from an OTC drug monograph on the basis of the Commissioner's determination that they would result in a drug product not being generally recognized as safe and effective or would result in misbranding. This order may include active ingredients for which no substantial comments in opposition to the advisory panel's proposed classification and no new data and information were received pursuant to § 330.10(a)(6)(iv) (21 CFR 330.10(a)(6)(iv)). Section 330.10(a)(7)(ii) authorizes the publication of a separate tentative order immediately following the close of the comment and new data periods for an advance notice of proposed rulemaking. However, in the case of the ingredients included in the proposal, the Commissioner waited until after proposed rulemakings were published and the periods for submission of comments and new data had ended. This additional period allowed the fullest possible opportunity for public comment and receipt of new data to upgrade the status of these ingredients.

As mentioned, no substantive comments or new data were submitted to support reclassification of any of these active ingredients to monograph status. Therefore, before a final rule on each respective drug category is published, the Commissioner has determined that these ingredients are not generally recognized as safe and effective and that any OTC drug product containing any of these active ingredients not be allowed to continue to be initially introduced or initially delivered for introduction into interstate commerce unless it is the subject of an approved application. FDA has elected to act on these ingredients in advance of finalization of other monograph conditions in order to expedite completion of the OTC drug review. Table I below lists the title, docket number, and active ingredients of the specific rulemakings that are addressed in this final rule.

FDA advises that the active ingredients listed in this final rule will not be included in the relevant final monographs because they have not been shown to be generally recognized as safe and effective for their intended use. The agency is amending 21 CFR part 310 to list all of the active ingredients covered by this final rule by adding them to § 310.545 (21 CFR 310.545). The agency further advises that these active ingredients should be eliminated from OTC drug products by November 10, 1993, regardless of whether further testing is undertaken to justify future use, and regardless of whether the relevant OTC drug monographs have been finalized at that time. Therefore, on or after November 10, 1993, no OTC drug product containing any ingredient listed in this final rule and included in § 310.545 either labeled or intended as an active ingredient for the uses specified in that section may be initially introduced or initially delivered for introduction into interstate commerce

unless it is the subject of an approved application. Further, any OTC drug product containing an ingredient subject to this final rule that is repackaged or relabeled after the effective date of this final rule must be in compliance with the final rule regardless of the date the product was initially introduced or initially delivered for introduction into interstate commerce. Manufacturers are urged to comply voluntarily with this final rule at the earliest possible date.

The agency points out that publication of this final rule does not preclude a manufacturer's testing an ingredient. New, relevant data can be submitted to the agency at a later date as the subject of an application that may provide for prescription or OTC marketing status. (See 21 CFR part 314.) As an alternative, where there are adequate data establishing general recognition of safety and effectiveness, such data may be submitted in an appropriate citizen petition to amend or establish a monograph, as appropriate. (See § 10.30 (21 CFR 10.30).) However, marketing of products containing these active ingredients may not continue while the data are being evaluated by the agency.

In response to the proposed rule on certain additional OTC Category II and III ingredients, nine drug manufacturers and six consumers submitted comments. Copies of the comments received are on public display in the Dockets Management Branch (HFA–305), Food and Drug Adminstration, rm. 1–23, 12420 Parklawn Dr., Rockville, MD 20857. Any additional information that has come to the agency's attention since publication of the proposed rule is also on public display in the Dockets Management Branch.

I. The Agency's Conclusions on the Comments

1. One comment requested clarification of the statement that any product containing any of the listed ingredients and labeled for an OTC use as identified by the proposed rule will be considered nonmonograph and misbranded under section 502 of the Federal Food, Drug, and Cosmetic Act (the act) (21 U.S.C. 352) (57 FR 38568 at 38572). The comment contended that this statement is limited in effect to the use of a listed ingredient as an active ingredient for the specified indication(s). Accordingly, this proposal does not extend to additional uses of the listed active ingredients covered by other OTC drug rulemaking proceedings.

The comment is correct. This final rule affects only the use of the listed ingredients as active ingredients for the specific indications under which they are listed. As stated in § 310.545, this rule is limited to "active ingredients" for various uses for which "* * * based on evidence currently available, there are inadequate data to establish general recognition of the safety and effectiveness of these ingredients for the specified uses: * * *."

2. One comment requested clarification of the agency's statement that "FDA has determined that the presence of these ingredients in an OTC drug product would result in that drug product not being generally recognized as safe and effective or would result in misbranding." (57 FR 38568). The comment contended that this statement applies only to the use of nonmonograph ingredients as active ingredients. The comment stated that certain nonmonograph ingredients may be used as inactive ingredients in product formulations, which should not cause the product to be misbranded, provided that no drug claims are made.

The agency's statement was made in the context of considering the affected ingredients as active ingredients. This final rule applies only to the use of the listed ingredients as active ingredients for the specific indications listed. The agency recognizes that some of the ingredients included in this final rule have valid uses as inactive ingredients (e.g., cinnamon oil, peppermint). Any inactive ingredient present in the product should have an appropriate purpose and be safe and suitable for use in the product in accordance with § 330.1(e) (21 CFR 330.1(e)). The presence of an appropriate inactive ingredient § 330.1(e) in a product will not cause the product to be misbranded, provided that no drug claims are attributed to the ingredient.

3. One comment requested that the proposed prohibition of salicylic acid in OTC topical antifungal drug products be expressly limited to its use as an active ingredient and not include its use as an adjuvant keratolytic in these drug products. The comment stated that following publication of the tentative final monograph for OTC topical antifungal drug products, additional data (Ref. 1) were submitted to that rulemaking on November 30, 1990, in support of salicylic acid as an adjuvant keratolytic in topical antifungal drug products. The comment stated that the criteria upon which the August 25, 1992, proposed rule is based are consonant with the characterization by agency personnel of the rulemaking as "administrative house cleaning" of ingredients no one is interested in. The comment contended that, from the standpoint of administrative procedural requirements, the criteria used by the agency to determine that an ingredient has been "abandoned" have not been met for salicylic acid as an adjuvant keratolytic.

The agency acknowledges that a submission of data was made on November 30, 1990. The agency reviewed that submission and informed the manufacturer in a letter dated February 15, 1991 (Ref. 2), that the "open, uncontrolled clinical trial does not provide any useful information." There were major flaws in the design of the clinical study. The agency stated in the August 25, 1992, proposal that no "substantive" comments or new data were submitted for the listed ingredients. The agency did not consider the November 30, 1990, data submission to be substantive. No other data were submitted to support monograph status for salicylic acid used as an adjuvant keratolytic in OTC topical antifungal drug products. Accordingly, the final rule does not contain an express limitation as requested by the comment.

References

(1) Comment No. C30, Docket No. 80N–0476, Dockets Management Branch.

(2) Letter from W. E. Gilbertson, FDA, to Guido Mendoza, Kramer Laboratories, Inc., coded LET24, Docket No. 80N–0476, Dockets Management Branch.

4. One comment requested that the agency delay its proposed action regarding benzoic acid and salicylic acid as active ingredients in OTC topical antifungal drug products. The comment acknowledged that substantive comments or adequate data have not been submitted to support benzoic acid and salicylic acid as Category I active ingredients for topical antifungal use. However, the comment stated that products containing these ingredients and labeled for the treatment of athletes foot and ringworm have been continuously marketed since 1932. The comment requested additional time to submit documentation and for an oral hearing.

Another comment requested that salsalate, an internal analgesic, antipyretic, and antirheumatic ingredient, be kept in Category III pending new studies and testing planned to be submitted before the final monograph. The comment stated that these studies would provide additional evidence of salsalate's OTC safety and efficacy.

The agency clearly stated in the proposal that "This proposal does not constitute a reopening of the administrative record or an opportunity to submit new data to any of the

specified rulemakings." (57 FR 38568). In addition, § 330.10(a)(7)(v) (21 CFR 330.10(a)(7)(v)) of the regulations governing the OTC drug review states that new data and information submitted after the closing of the administrative record for a tentative final rule "* * * but prior to the establishment of a final monograph will be considered as a petition to amend the monograph and will be considered by the Commissioner only after a final monograph has been published in the **Federal Register** unless the Commissioner finds that good cause has been shown that warrants earlier consideration."

None of the comments offered good cause why the requested ingredients should not be included in this final rule. Benzoic acid and salicylic acid have been under consideration in the rulemaking for OTC topical antifungal drug products since 1974. The comment did not provide any explanation why data or comments were not submitted before the close of the administrative record on February 12, 1991. Salsalate has been under consideration in the rulemaking for OTC internal analgesic, antipyretic, and antirheumatic drug products since 1972. The comment did not provide any explanation why the data were not submitted before the close of the administrative record on January 16, 1990. The appropriate course of action for both comments is to submit any new data to the specific rulemaking for that class of OTC drug products, in a citizen petition under §§ 10.30 and 330.10.

5. Seven comments objected to the proposed rulemaking as a ban on vitamin, mineral, and other natural food supplements. The comments were concerned that many nutritional supplements and herbs would be removed from the marketplace. One comment contended that a number of the ingredients (pyridoxine hydrochloride, betaine hycrochloride, papaya, capsicum, eucalyptus oil, hydrogen peroxide, calcium pantothenate, and riboflavin) have nutritional value. Two of the comments contended that the agency is ignoring the Proxmire Act of 1976 that instructed FDA to set up separate guidelines for dietary supplements.

The agency recognizes that some of the ingredients included in this rulemaking are also marketed as vitamins, minerals, and food supplements. This rule affects only the marketing of ingredients listed as active ingredients in specific types of OTC drug products for which unproven medical claims are being made. This rule does not affect the continued use and marketing of these ingredients in vitamin, mineral, and food supplement products and, thus, is in conformance with the 1976 amendment to the act (21 U.S.C. 350). The agency believes that the comments misinterpreted the agency's intent as a ban on the substance itself rather than a restriction on marketing ingredients with claims as an active ingredient for specific listed drug indications.

6. Three comments disagreed with the proposed listing of aspergillus oryza enzymes under digestive aid drug products in § 310.545(a)(8)(ii). One comment stated that the term describes a group of functionally different enzymes derived from a particular source. Another comment mentioned that there is no evidence that "aspergillus oryza enzymes" have been used in OTC drug products in the past or at the present time, and that inclusion in the listing appears inappropriate. Several comments stated that new information on lactase enzyme derived from *Aspergillus oryzae (A. oryzae)* had been submitted to the administrative record in the rulemaking for OTC digestive aid drug products. Thus, the comments contended that aspergillus oryza enzymes should be deleted from the list of nonmonograph ingredients until the digestive aid drug products rulemaking is completed, or if retained in the list, the agency should clarify that it does not include lactase enzyme derived from *A. oryzae*.

Aspergillus oryza enzymes were included in the listing in proposed § 310.545(a)(8)(ii) based on their listing in a call-for-data notice published in the **Federal Register** of August 27, 1975 (40 FR 38179), and the Panel's statement that it was neither able to locate nor was it aware of any significant body of data demonstrating the safety and effectiveness of aspergillus oryza enzymes for treating the symptoms of intestinal distress (47 FR 454 at 458, January 5, 1982). As one comment noted, the term describes a group of functionally different enzymes derived from a particular source. Lactase enzyme is the only enzyme derived from *A. oryzae* for which the agency has received any data in the rulemaking for OTC digestive aid drug products. The comments are correct in stating that this particular enzyme should be excluded from this final rule. Accordingly, the agency is including a parenthetical phrase in the regulation following aspergillus oryza enzymes that states: "(except lactase enzymes derived from *Aspergillus oryzae*)."

7. One comment requested clarification of the status of camphor and menthol as external analgesic, anesthetic, and antipruritic active ingredients in fever blister and cold sore treatment drug products because of the listing of these ingredients in proposed § 310.545(a)(10)(v).

The proposed rule for OTC external analgesic fever blister and cold sore treatment drug products (55 FR 3370 at 3382 and 3383, January 31, 1990) provides that products containing ingredients listed in § 348.10(a) or (b) or combinations of ingredients identified in § 348.20(a)(1) or (a)(3) may be labeled "for * * * pain and itching associated with fever blisters and cold sores." Proposed § 348.10(b)(2) and (b)(6) of the tentative final monograph for OTC external analgesic drug products (48 FR 5852 at 5867, February 8, 1983) list camphor at 0.1 to 3 percent and menthol at 0.1 to 1 percent, respectively. Camphor and menthol are also listed in § 348.12(b)(1) and (b)(2) at higher concentrations for counterirritant use.

The August 25, 1992 proposed rule that listed camphor and menthol in § 310.545(a)(10)(v) was intended to apply to the higher (counterirritant) concentrations of camphor and menthol only. The agency is clarifying this fact in this final rule by adding in § 310.545(a)(10)(v) the parenthetical phrase "(exceeding 3 percent)" after the entry for camphor and by adding the parenthetical phrase "(exceeding 1 percent)" after the entry for menthol.

II. Summary of Significant Changes From the Proposed Rule

1. The agency is including a parenthetical phrase following aspergillus oryza enzymes in § 310.545(a)(8)(ii) that states: "(except lactase enzymes derived from *Aspergillus oryzae*)." (See comment 6.)

2. The agency is adding in § 310.545(a)(10)(v) the parenthetical phrase "(exceeding 3 percent)" after the entry for camphor and adding the parenthetical phrase "(exceeding 1 percent)" after the entry for menthol. (See comment 7.)

3. The agency is redesignating several of the proposed paragraphs in § 310.545 of this final rule as follows:

Proposed rule	Final rule
(a)(21)(i)	(a)(22)(ii)
(a)(22) through (a)(24).	(a)(23) through (a)(25)
(d)(4)	(d)(11)

III. The Agency's Final Conclusions on Certain Additional OTC Drug Category II and III Active Ingredients

The agency has determined that no substantive comments or additional data have been submitted to the OTC drug

review to support any of the ingredients listed below as being generally recognized as safe and effective for the OTC drug uses specified in the table (Table I). Based on the agency's procedural regulations (21 CFR 330.10(a)(7)(ii)), the agency has determined that these ingredients are not generally recognized as safe and effective and are misbranded when present in the following specific OTC drug products:

TABLE I.—OTC DRUG RULEMAKINGS AND ACTIVE INGREDIENTS COVERED BY THIS NOTICE

Rulemaking
(1) Digestive Aid Drug Products (Docket No. 81N–0106):
Alcohol
Aluminum hydroxide
Amylase
Anise seed
Aromatic powder
Asafetida
Aspergillus oryza enzymes (except lactase enzyme derived from *Aspergillus oryzae*)
Bacillus acidophilus
Bean
Belladonna alkaloids
Belladonna leaves, powdered extract
Betaine hydrochloride
Bismuth subcarbonate
Bismuth subgallate
Black radish powder
Blessed thistle (cnicus benedictus)
Buckthorn
Calcium gluconate
Capsicum
Capsicum, fluid extract of
Carbon
Cascara sagrada extract
Catechu, tincture
Catnip
Chamomile flowers
Charcoal, wood
Chloroform
Cinnamon oil
Cinnamon tincture
Citrus pectin
Diastase
Diastase malt
Dog grass
Elecampane
Ether
Fennel acid
Galega
Ginger
Glycine
Hydrastis canadensis (golden seal)
Hectorite
Horsetail
Huckleberry
Hydrastis fluid extract
Hydrochloric acid
Iodine
Iron ox bile
Johnswort
Juniper
Kaolin, colloidal
Knotgrass
Lactic acid
Lactose
Lavender compound, tincture of
Linden
Lipase
Lysine hydrochloride
Mannitol
Mycozyme
Myrrh, fluid extract of
Nettle
Nickel-pectin
Nux vomica extract
Orthophosphoric acid
Papaya, natural
Pectin
Peppermint
Peppermint spirit
Phenacetin
Potassium bicarbonate
Potassium carbonate
Protease
Prolase
Rhubarb fluid extract
Senna
Sodium chloride
Sodium salicylate
Stem bromelain
Strawberry
Strychnine
Tannic acid
Trillium
Woodruff
(2) External Analgesic Drug Products:
(a) Fever Blister and Cold Sore Treatment Drug Products (Docket No. 78N–301F):
Allyl isothiocyanate
Aspirin
Bismuth sodium tartrate
Camphor (exceeding 3 percent)
Capsaicin
Capsicum
Capsicum oleoresin
Chloral hydrate
Chlorobutanol
Cyclomethycaine sulfate
Eucalyptus oil
Eugenol
Glycol salicylate
Hexylresorcinol
Histamine dihydrochloride
Menthol (exceeding 1 percent)
Methapyrilene hydrochloride
Methyl nicotinate
Methyl salicylate
Pectin
Salicylamide
Strong ammonia solution
Tannic acid
Thymol
Tripelennamine hydrochloride
Trolamine salicylate
Turpentine oil
Zinc sulfate
(b) Insect Bite and Sting Drug Products (Docket No. 78N–301P):
Alcohol
Alcohol, ethoxylated alkyl
Benzalkonium chloride
Calamine
Ergot fluidextract
Ferric chloride
Panthenol
Peppermint oil
Pyrilamine maleate
Sodium borate
Trolamine salicylate
Turpentine oil
Zinc oxide
Zirconium oxide
(c) Poison Ivy, Poison Oak, and Poison Sumac Drug Products (Docket No. 78N–301P):
Alcohol
Aspirin
Benzethonium chloride
Benzocaine (0.5 to 1.25 percent)
Bithionol
Calamine
Cetalkonium chloride
Chloral hydrate
Chlorobutanol
Chlorpheniramine maleate
Creosote, beechwood
Cyclomethycaine sulfate
Dexpanthenol
Diperodon hydrochloride
Eucalyptus oil
Eugenol
Glycerin
Glycol salicylate
Hectorite
Hexylresorcinol
Hydrogen peroxide
Impatiens biflora tincture
Iron oxide
Isopropyl alcohol
Lanolin
Lead acetate
Merbromin
Mercuric chloride
Methapyriiene hydrochloride
Panthenol
Parethoxycaine hydrochloride
Phenyltoloxamine dihydrogen citrate
Povidone-vinylacetate copolymers
Pyrilamine maleate
Salicylamide
Salicylic acid
Simethicone
Sulfur
Tannic acid
Thymol
Trolamine salicylate
Turpentine oil
Zirconium oxide
Zyloxin
(3) Skin Protectant Drug Products:
(a) Astringent Drug Products (Docket No. 78N–021A):
Acetone
Alcohol
Alum, ammonium
Alum, potassium
Aluminum chlorhydroxy complex
Aromatics
Benzalkonium chloride

TABLE I.—OTC DRUG RULEMAKINGS AND ACTIVE INGREDIENTS COVERED BY THIS NOTICE—Continued

Rulemaking
Benzethonium chloride
Benzocaine
Benzoic acid
Boric acid
Calcium acetate
Camphor gum
Clove oil
Colloidal oatmeal
Cresol
Cupric sulfate
Eucalyptus oil
Eugenol
Honey
Isopropyl alcohol
Menthol
Methyl salicylate
Oxyquinoline sulfate
P-t-butyl-m-cresol
Peppermint oil
Phenol
Polyoxyethylene laurate
Potassium ferrocyanide
Sage oil
Silver nitrate
Sodium borate
Sodium diacetate
Talc
Tannic acid glycerite
Thymol
Topical starch
Zinc chloride
Zinc oxide
Zinc phenolsulfonate
Zinc stearate
Zinc sulfate
(b) Diaper Rash Drug Products (Docket No. 78N–021D):
Aluminum hydroxide
Cocoa butter
Cysteine hydrochloride
Glycerin
Protein hydrolysate
Racemethionine
Sulfur
Tannic acid
Zinc acetate
Zinc carbonate
(c) Fever Blister and Cold Sore Treatment Drug Products (Docket No. 78N–021F):
Bismuth subnitrate
Boric acid
Pyridoxide hydrochloride
Sulfur
Tannic acid
Topical starch
Trolamine
Zinc sulfate
(d) Insect Bite and Sting Drug Products (Docket No. 78N–021P):
Alcohol
Alcohol, ethoxylated alkyl
Ammonia solution, strong
Ammonium hydroxide
Benzalkonium chloride
Camphor
Ergot fluidextract
Ferric chloride
Menthol

TABLE I.—OTC DRUG RULEMAKINGS AND ACTIVE INGREDIENTS COVERED BY THIS NOTICE—Continued

Rulemaking
Peppermint oil
Phenol
Pyrilamine maleate
Sodium borate
Trolamine
Turpentine oil
Zirconium oxide
(e) Poison Ivy, Poison Oak, and Poison Sumac Drug Products (Docket No. 78N–021P):
Alcohol
Anion and cation exchange resins buffered
Benzethonium chloride
Benzocaine
Benzyl alcohol
Bismuth subnitrate
Bithionol
Boric acid
Camphor
Cetalkonium chloride
Chloral hydrate
Chlorpheniramine maleate
Creosote
Diperodon hydrochloride
Diphenhydramine hydrochloride
Eucalyptus oil
Ferric chloride
Glycerin
Hectorite
Hydrogen peroxide
Impatiens biflora tincture
Iron oxide
Isopropyl alcohol
Lanolin
Lead acetate
Lidocaine
Menthol
Merbromin
Mercuric chloride
Panthenol
Parethoxycaine hydrochloride
Phenol
Phenyltoloxamine dihydrogen citrate
Povidone-vinylacetate copolymers
Salicylic acid
Simethicone
Tannic acid
Topical starch
Trolamine
Turpentine oil
Zirconium oxide
Zyloxin
(4) Topical Antifungal Drug Products (Docket No. 80N–0476):
Alcloxa
Alum, potassium
Aluminum sulfate
Amyltricresols, secondary
Basic fuchsin
Benzethonium chloride
Benzoic acid
Benzoxiquine
Boric acid
Camphor
Candicidin
Chlorothymol
Coal tar

TABLE I.—OTC DRUG RULEMAKINGS AND ACTIVE INGREDIENTS COVERED BY THIS NOTICE—Continued

Rulemaking
Dichlorophen
Menthol
Methylparaben
Oxyquinoline
Oxyquinoline sulfate
Phenol
Phenolate sodium
Phenyl salicylate
Propionic acid
Propylparaben
Resorcinol
Salicylic acid
Sodium borate
Sodium caprylate
Sodium propionate
Sulfur
Tannic acid
Thymol
Tolindate
Triacetin
Zinc caprylate
Zinc propionate
(5) Internal Analgesic Drug Products (Docket No. 77N–0094):
Aminobenzoic acid[1]
Antipyrine
Aspirin, aluminum
Calcium salicylate
Codeine
Codeine phosphate
Codeine sulfate
Iodoantipyrine
Lysine aspirin
Methapyrilene fumarate[1]
Phenacetin
Pheniramine maleate[1]
Pyrilamine maleate[1]
Quinine
Salsalate
Sodium aminobenzoate[1]
(6) Orally Administered Menstrual Drug Products (Docket No. 82N–0165):
Alcohol
Alfalfa leaves
Aloes
Asclepias tuberosa
Asparagus
Barosma
Bearberry (extract of uva ursi)
Bearberry fluidextract (extract of bearberry)
Blessed thistle (cnicus benedictus)
Buchu powdered extract (extract of buchu)
Calcium lactate
Calcium pantothenate
Capsicum oleoresin
Cascara fluidextract, aromatic (extract of cascara)
Chlorprophenpyridamine maleate
Cimicifuga racemosa
Codeine
Collinsonia (extract stone root)
Corn silk
Couch grass
Dog grass extract
Ethyl nitrite
Ferric chloride

TABLE I.—OTC DRUG RULEMAKINGS AND ACTIVE INGREDIENTS COVERED BY THIS NOTICE—Continued

Rulemaking
Ferrous sulfate
Gentiana lutea (gentian)
Glycyrrhiza (licorice)
Homatropine methylbromide
Hydrangea, powdered extract (extract of hydrangea)
Hydrastis canadensis (golden seal)
Hyoscyamine sulfate
Juniper oil (oil of juniper)
Magnesium sulfate
Methapyrilene hydrochloride
Methenamine
Methylene blue
Natural estrogenic hormone
Niacinamide
Nutmeg oil (oil of nutmeg)
Oil of erigeron
Parsley
Peppermint spirit
Pepsin, essence
Phenacetin
Phenindamine tartrate
Phenyl salicylate
Piscidia erythrina
Pipsissewa
Potassium acetate
Potassium nitrate
Riboflavin
Saw palmetto
Senecio aureus
Sodium benzoate
Sodium nitrate
Sucrose
Sulfurated oils of turpentine
Taraxacum officinale
Theobromine sodium salicylate
Theophylline
Thiamine hydrochloride
Triticum
Turpentine, venice (venice turpentine)
Urea
(7) Pediculicide Drug Products (Docket No. 81N–0201):
Benzocaine
Benzyl alcohol
Benzyl benzoate
Chlorophenothane (dichlorodiphenyl trichloroethane)
Coconut oil soap, aqueous
Copper oleate
Docusate sodium
Formic acid[2]
Isobornyl thiocyanoacetate
Picrotoxin
Propylene glycol
Sabadilla alkaloids
Sulfur, sublimed
Thiocyanoacetate

[1] Ingredient used as an analgesic-antipyretic adjuvant.

[2] This ingredient was not submitted to or previously classified in the OTC drug review, but has been observed in a marketed product.

Accordingly, any drug product containing any of these ingredients either labeled or intended as an active ingredient for any of the OTC uses identified above will be considered nonmonograph and misbranded under section 502 of the act (21 U.S.C. 352) and a new drug under section 201(p) of the act (21 U.S.C. 321(p)) for which an approved application or abbreviated application under section 505 of the act (21 U.S.C. 355) and 21 CFR part 314 of the regulations is required for marketing. As an alternative, where there are adequate data establishing general recognition of safety and effectiveness, such data may be submitted in a citizen petition to amend the appropriate monograph to include any of the above active ingredients in OTC drug products. (See 21 CFR 10.30.)

Any OTC drug product containing any of the above ingredients either labeled or intended as an active ingredient for the uses included in the above rulemakings that is initially introduced or initially delivered for introduction into interstate commerce after November 10, 1993 and that is not the subject of an approved application or abbreviated application will be in violation of sections 502 and 505 of the act (21 U.S.C. 352 and 355) and, therefore, subject to regulatory action. Further, any OTC drug product containing an ingredient subject to this rulemaking that is repackaged or relabeled after November 10, 1993 must be in compliance with the rule regardless of the date the product was initially introduced or intitially delivered for introduction into interstate commerce. Manufacturers are encouraged to comply voluntarily with the rule at the earliest possible date.

No comments were received in response to the agency's request for specific comment on the economic impact of this rulemaking (57 FR 38568 at 38572). The agency concludes that there is no basis for the continued marketing of these ingredients for the uses listed in Table I above. There are other ingredients being considered for monograph status that manufacturers can use to reformulate affected products. In many instances, manufacturers have already reformulated their products to include these ingredients. As a result of this final rule, manufacturers may need to reformulate some products prior to promulgation of the applicable final monograph. However, there will be no additional costs because reformulation would be required, in any event, when the final monograph is published.

Early finalization of the nonmonograph status of the ingredients listed in this notice will benefit both consumers and manufacturers. Consumers will benefit from the early removal from the marketplace of ingredients for which safety and effectiveness have not been established. This action will result in a direct economic savings to consumers. Manufacturers will benefit from being able to use alternative ingredients that are under review to determine general recognition of safety and effectiveness, without incurring additional expense of clinical testing for these ingredients. Based on the above, the agency certifies that this final rule will not have a significant economic impact on a substantial number of small entities.

The agency has determined under 21 CFR 25.24(c)(6) that this action is of a type that does not individually or cumulatively have a significant effect on the human environment. Therefore, neither an environmental assessment nor an environmental impact statement is required.

List of Subjects in 21 CFR Part 310

Administrative practice and procedure, Drugs, Labeling, Medical devices, Reporting and recordkeeping requirements.

Therefore, under the Federal Food, Drug, and Cosmetic Act and under authority delegated to the Commissioner of Food and Drugs, 21 CFR part 310 is amended as follows:

PART 310—NEW DRUGS

1. The authority citation for 21 CFR part 310 continues to read as follows:

Authority: Secs. 201, 301, 501, 502, 503, 505, 506, 507, 512–516, 520, 601(a), 701, 704, 705, 706 of the Federal Food, Drug, and Cosmetic Act (21 U.S.C. 321, 331, 351, 352, 353, 355, 356, 357, 360b-360f, 360j, 361(a), 371, 374, 375, 376); secs. 215, 301, 302(a), 351, 354–360F of the Public Health Service Act (42 U.S.C. 216, 241, 242(a), 262, 263b-263n).

2. Section 310.545 is amended by redesignating the text of paragraphs (a)(8) and (a)(18) as paragraphs (a)(8)(i) and (a)(18)(i), respectively; by adding new (a)(8)(i) heading, (a)(8)(ii), (a)(10)(v) through (a)(10)(vii), (a)(18)(i) heading, (a)(18)(ii) through (a)(18)(vi), (a)(22)(ii), (a)(23) through (a)(25), and (d)(11); and by revising paragraph (d) introductory text and paragraph (d)(1) to read as follows:

§ 310.545 Drug products containing certain active ingredients offered over-the-counter (OTC) for certain uses.

(a) * * *

(8) *Digestive aid drug products*—(i) *Approved as of May 7, 1991.* * * *

(ii) *Approved as of November 10, 1993.*

Alcohol
Aluminum hydroxide

Amylase
Anise seed
Aromatic powder
Asafetida
Aspergillus oryza enzymes (except lactase enzyme derived from *Aspergillus oryzae*)
Bacillus acidophilus
Bean
Belladonna alkaloids
Belladonna leaves, powdered extract
Betaine hydrochloride
Bismuth subcarbonate
Bismuth subgallate
Black radish powder
Blessed thistle (cnicus benedictus)
Buckthorn
Calcium gluconate
Capsicum
Capsicum, fluid extract of
Carbon
Cascara sagrada extract
Catechu, tincture
Catnip
Chamomile flowers
Charcoal, wood
Chloroform
Cinnamon oil
Cinnamon tincture
Citrus pectin
Diastase
Diastase malt
Dog grass
Elecampane
Ether
Fennel acid
Galega
Ginger
Glycine
Hydrastis canadensis (golden seal)
Hectorite
Horsetail
Huckleberry
Hydrastis fluid extract
Hydrochloric acid
Iodine
Iron ox bile
Johnswort
Juniper
Kaolin, colloidal
Knotgrass
Lactic acid
Lactose
Lavender compound, tincture of
Linden
Lipase
Lysine hydrochloride
Mannitol
Mycozyme
Myrrh, fluid extract of
Nettle
Nickel-pectin
Nux vomica extract
Orthophosphoric acid
Papaya, natural
Pectin
Peppermint
Peppermint spirit
Phenacetin
Potassium bicarbonate
Potassium carbonate
Protease
Prolase
Rhubarb fluid extract
Senna
Sodium chloride
Sodium salicylate
Stem bromelain
Strawberry
Strychnine
Tannic acid
Trillium
Woodruff

* * * * *

(10) * * *

(v) *Fever blister and cold sore treatment drug products.*

Allyl isothiocyanate
Aspirin
Bismuth sodium tartrate
Camphor (exceeding 3 percent)
Capsaicin
Capsicum
Capsicum oleoresin
Chloral hydrate
Chlorobutanol
Cyclomethycaine sulfate
Eucalyptus oil
Eugenol
Glycol salicylate
Hexylresorcinol
Histamine dihydrochloride
Menthol (exceeding 1 percent)
Methapyrilene hydrochloride
Methyl nicotinate
Methyl salicylate
Pectin
Salicylamide
Strong ammonia solution
Tannic acid
Thymol
Tripelennamine hydrochloride
Trolamine salicylate
Turpentine oil
Zinc sulfate

(vi) *Insect bite and sting drug products.*

Alcohol
Alcohol, ethoxylated alkyl
Benzalkonium chloride
Calamine
Ergot fluidextract
Ferric chloride
Panthenol
Peppermint oil
Pyrilamine maleate
Sodium borate
Trolamine salicylate
Turpentine oil
Zinc oxide
Zirconium oxide

(vii) *Poison ivy, poison oak, and poison sumac drug products.*

Alcohol
Aspirin
Benzethonium chloride
Benzocaine (0.5 to 1.25 percent)
Bithionol
Calamine
Cetalkonium chloride
Chloral hydrate
Chlorobutanol
Chlorpheniramine maleate
Creosote, beechwood
Cyclomethycaine sulfate
Dexpanthenol
Diperodon hydrochloride
Eucalyptus oil
Eugenol
Glycerin
Glycol salicylate
Hectorite
Hexylresorcinol
Hydrogen peroxide
Impatiens biflora tincture
Iron oxide
Isopropyl alcohol
Lanolin
Lead acetate
Merbromin
Mercuric chloride
Methapyrilene hydrochloride
Panthenol
Parethoxycaine hydrochloride
Phenyltoloxamine dihydrogen citrate
Povidone-vinylacetate copolymers
Pyrilamine maleate
Salicylamide
Salicylic acid
Simethicone
Sulfur
Tannic acid
Thymol
Trolamine salicylate
Turpentine oil
Zirconium oxide
Zyloxin

* * * * *

(18) *Skin protectant drug products—*

(i) Ingredients. * * *

(ii) *Astringent drug products.*

Acetone
Alcohol
Alum, ammonium
Alum, potassium
Aluminum chlorhydroxy complex
Aromatics
Benzalkonium chloride
Benzethonium chloride
Benzocaine
Benzoic acid
Boric acid
Calcium acetate
Camphor gum
Clove oil
Colloidal oatmeal
Cresol
Cupric sulfate
Eucalyptus oil
Eugenol
Honey
Isopropyl alcohol
Menthol
Methyl salicylate
Oxyquinoline sulfate
P-t-butyl-m-cresol
Peppermint oil
Phenol
Polyoxeythylene laurate
Potassium ferrocyanide
Sage oil
Silver nitrate
Sodium borate
Sodium diacetate
Talc
Tannic acid glycerite
Thymol
Topical starch
Zinc chloride
Zinc oxide
Zinc phenolsulfonate
Zinc stearate
Zinc sulfate

(iii) *Diaper rash drug products.*

Aluminum hydroxide

Cocoa butter
Cysteine hydrochloride
Glycerin
Protein hydrolysate
Racemethionine
Sulfur
Tannic acid
Zinc acetate
Zinc carbonate

(iv) *Fever blister and cold sore treatment drug products.*

Bismuth subnitrate
Boric acid
Pyridoxine hydrochloride
Sulfur
Tannic acid
Topical starch
Trolamine
Zinc sulfate

(v) *Insect bite and sting drug products.*

Alcohol
Alcohol, ethoxylated alkyl
Ammonia solution, strong
Ammonium hydroxide
Benzalkonium chloride
Camphor
Ergot fluidextract
Ferric chloride
Menthol
Peppermint oil
Phenol
Pyrilamine maleate
Sodium borate
Trolamine
Turpentine oil
Zinc oxide

(vi) *Poison ivy, poison oak, and poison sumac drug products.*

Alcohol
Anion and cation exchange resins buffered
Benzethonium chloride
Benzocaine
Benzyl alcohol
Bismuth subnitrate
Bithionol
Boric acid
Camphor
Cetalkonium chloride
Chloral hydrate
Chlorpheniramine maleate
Creosote
Diperodon hydrochloride
Diphenhydramine hydrochloride
Eucalyptus oil
Ferric chloride
Glycerin
Hectorite
Hydrogen peroxide
Impatiens biflora tincture
Iron oxide
Isopropyl alcohol
Lanolin
Lead acetate
Lidocaine
Menthol
Merbromin
Mercuric chloride
Panthenol
Parethoxycaine hydrochloride
Phenol
Polymyxin B sulfomethoxamine dihydrogen citrate
Polyvidone-vinylacetate copolymers
Salicylic acid
Simethicone
Tannic acid
Topical starch
Trolamine
Turpentine oil
Zirconium oxide
Zyloxin

* * * * *

(22) * * *

(ii) *Ingredients.*

Alcloxa
Alum, potassium
Aluminum sulfate
Amyltricresols, secondary
Basic fuchsin
Benzethonium chloride
Benzoic acid
Benzoxiquine
Boric acid
Camphor
Candicidin
Chlorothymol
Coal tar
Dichlorophen
Menthol
Methylparaben
Oxyquinoline
Oxyquinoline sulfate
Phenol
Phenolate sodium
Phenyl salicylate
Propionic acid
Propylparaben
Resorcinol
Salicylic acid
Sodium borate
Sodium caprylate
Sodium propionate
Sulfur
Tannic acid
Thymol
Tolindate
Triacetin
Zinc caprylate
Zinc propionate

(23) *Internal analgesic drug products.*

Aminobenzoic acid
Antipyrine
Aspirin, aluminum
Calcium salicylate
Codeine
Codeine phosphate
Codeine sulfate
Iodoantipyrine
Lysine aspirin
Methapyrilene fumarate
Phenacetin
Pheniramine maleate
Pyrilamine maleate
Quinine
Salsalate
Sodium aminobenzoate

(24) *Orally administered menstrual drug products.*

Alcohol
Alfalfa leaves
Aloes
Asclepias tuberosa
Asparagus
Barosma
Bearberry (extract of uva ursi)
Bearberry fluidextract (extract of bearberry)
Blessed thistle (cnicus benedictus)
Buchu powdered extract (extract of buchu)
Calcium lactate
Calcium pantothenate
Capsicum oleoresin
Cascara fluidextract, aromatic (extract of cascara)
Chlorprophenpyridamine maleate
Cimicifuga racemosa
Codeine
Collinsonia (extract stone root)
Corn silk
Couch grass
Dog grass extract
Ethyl nitrite
Ferric chloride
Ferrous sulfate
Gentiana lutea (gentian)
Glycyrrhiza (licorice)
Homatropine methylbromide
Hydrangea, powdered extract (extract of hydrangea)
Hydrastis canadensis (golden seal)
Hyoscyamine sulfate
Juniper oil (oil of juniper)
Magnesium sulfate
Methapyrilene hydrochloride
Methenamine
Methylene blue
Natural estrogenic hormone
Niacinamide
Nutmeg oil (oil of nutmeg)
Oil of erigeron
Parsley
Peppermint spirit
Pepsin, essence
Phenacetin
Phenindamine tartrate
Phenyl salicylate
Piscidia erythrina
Pipsissewa
Potassium acetate
Potassium nitrate
Riboflavin
Saw palmetto
Senecio aureus
Sodium benzoate
Sodium nitrate
Sucrose
Sulferated oils of turpentine
Taraxacum officinale
Theobromine sodium salicylate
Theophylline
Thiamine hydrochloride
Triticum
Turpentine, venice (venice turpertine)
Urea

(25) *Pediculicide drug products.*

Benzocaine
Benzyl alcohol
Benzyl benzoate
Chlorophenothane (dichlorodiphenyl trichloroethane)
Coconut oil soap, aqueous
Copper oleate
Docusate sodium
Formic acid
Isobornyl thiocyanoacetate
Picrotoxin
Propylene glycol
Sabadilla alkaloids
Sulfur, sublimed
Thiocyanoacetate

* * * * *

(d) Any OTC drug product that is not in compliance with this section is

subject to regulatory action if initially introduced or initially delivered for introduction into interstate commerce after the dates specified in paragraphs (d)(1) through (d)(11) of this section.

(1) May 7, 1991, for products subject to paragraphs (a)(1) through (a)(6)(i)(A), (a)(6)(ii), (a)(7) (except as covered by paragraph (d)(3) of this section), (a)(8)(i), (a)(9) through (a)(10)(iii), (a)(11) through (a)(18)(i), and (a)(19) of this section.

* * * * *

(11) November 10, 1993, for products subject to paragraphs (a)(8)(ii), (a)(10)(v) through (a)(10)(vii), (a)(18)(ii) through (a)(18)(vi), (a)(22)(ii), and (a)(23) through (a)(25) of this section.

Dated: March 31, 1993.

Michael R. Taylor,

Deputy Commissioner for Policy.

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